BRIEF REPORT

Risk of Thromboembolic Events Following COVID-19 Diagnosis Without Hospitalization

Katherine Schreck, MD, Caroline Carlin, PhD, and Jason Ricco, MD, MPH

Introduction: **Current research shows no increased risk of thromboembolic events with mild COVID-19 but does not account for comorbidities. The aim of this study was to examine the incidence of thromboembolic events, including pulmonary embolism, cerebral infarction, and deep vein thrombosis, in nonhospitalized patients diagnosed with COVID-19 while accounting for comorbidities such as diabetes, asthma, COPD and cancer.**

Methods: **We completed a large retrospective observational analysis of adult patients within a large urban health system.**

Results: **Using a logit framework (with and without propensity score weighting), there was no increased risk of thromboembolic events among patients positive for SARS-CoV-2 who did not require hospitalization for COVID-19.**

Conclusion: **This data suggest prophylactic anticoagulation is likely not warranted in the outpatient setting. (J Am Board Fam Med 2022;35:1163–1167.)**

Keywords: **Anticoagulants, COVID-19, Incidence, Retrospective Studies, SARS-CoV-2, Urban Health, Venous Thromboembolism**

Introduction

Venous thromboembolism (VTE) is a major complication from COVID-19 infection among patients hospitalized with COVID-19, particularly among those critically ill and requiring intensive care.[1–3] As a result, both therapeutic and prophylactic anticoagulation interventions have been studied and implemented in hospitals to prevent VTE complications.[1,4,5] Despite comprising the largest population infected with COVID-19, less is known about VTE risk among patients not requiring hospitalization. A retrospective cohort study found that the 30-day incidence of outpatient VTE among symptomatic patients with positive SARS-CoV-2 test results was similar to that of patients with negative results, but did not control for other risk factors for VTE.[6] Our study addresses this limitation by measuring risk of outpatient VTE due to COVID-19 while accounting for comorbidities and other confounding factors.

Methods

The patient population for this retrospective observational study was drawn from the electronic health records of a large urban multispecialty health system. To be included in the study, the patient must be between the ages of 18 and 75 and have at least 2 encounters with the health care system from January to December of 2020. Patients who had opted out of research were excluded. The University of Minnesota institutional review board approved the study under expedited review and waived the consent process.

ICD10 codes and lab results were used to identify patient populations in our data. A COVID-19 diagnosis was defined as a 'positive' or 'detected' test result. Patients were presumed negative if no

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From Department of Family Medicine and Community Health, University of Minnesota Medical School, Minneapolis, MN (KS, CC, JR).

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Corresponding author: Jason Ricco, MD, MPH, Broadway Family Medicine, 2426 West Broadway Ave, Minneapolis, MN 55411. Phone: 612-302-8200. Fax: 612-302-8275 (E-mail: ricco004@umn.edu).

result was available in the time period above. A thromboembolic event was defined as a diagnosis with an ICD10 code including 'thrombosis', 'embolism' or 'cerebral infarction'. Hospitalization due to COVID-19 was defined as a hospital stay within 90 days of a positive COVID-19 test with any of the following diagnoses associated with the admission: viral pneumonia, acute respiratory distress syndrome, respiratory failure, coronavirus or COVID-19. Comorbidities to be investigated were determined by the research team based on literature review and clinical experience and identified by ICD10 codes. The research team intended to account for medication use such as hormones or anticoagulants, however the accessible chart could not provide reliable data for these measures.

We modeled the incidence of a thromboembolic event using a multivariate logit regression. To add additional controls for a patient's propensity to be in the treatment group (ie, to have a positive COVID-19 diagnosis that did not lead to hospitalization), we tested the impact of including inverse propensity score weighting to the logit regression.

After estimating the thromboembolic event model, we used the results to predict the average marginal effect of a COVID-19 diagnosis on the probability of a thromboembolic event. The marginal effect is defined as the predicted change in the probability of a thromboembolic event when a COVID-19 diagnosis without hospitalization occurs, holding all other patient characteristics constant.

Results

A summary of our study sample can be found in Table 1. The statistical significance of differences in the characteristics of those with a positive COVID-19 diagnosis, but no hospitalization, relative to the control group, is indicated by the p-values included in the table. Those with the positive COVID-19 diagnosis tended to be younger, less white, less likely to prefer English, more likely to be foreign born, and have a higher body mass index. Their neighborhoods tended to be less educated and have higher poverty rates. There was no consistent pattern by chronic condition of incidence of COVID-19 without hospitalization.

The results of our model of thromboembolic events are shown in Table 2. The top panel of the table shows the average marginal effect of COVID-19 without hospitalization. The bottom panel shows the full set of estimated logit coefficients. The impact of the diagnosis had no statistically significant effect on the risk of a thromboembolic event, with ($P = .924$) or without ($P = .912$) inverse propensity score weighting. The addition of propensity score weights had little impact on the results.

Discussion

Our large retrospective analysis supports earlier data that patients diagnosed with SARS-CoV-2 who do not require hospitalization are not at increased risk for thromboembolic events.[6] Our results are also concordant with the ACTIV-4B Outpatient Thrombosis Trial which was terminated early due to lower than anticipated event rates in the outpatient setting.[7] Adding to the existing literature, our study thoroughly investigated the impact of comorbidities and possible confounding factors on thromboembolic event risk by using robust propensity score matching. In this way, we feel confident in our conclusion that cases of COVID-19 not requiring hospitalization do not put patients at increased risk for thromboembolic events.

Our study showed Black patients were at statistically significant increased risk of COVID-19, regardless of hospitalization status ($P = .002$ for +COVID-19 not leading to hospitalization; $P < 0.001$ for +COVID-19 regardless of hospitalization). This finding is consistent with previous studies showing higher rates of infection among Black and Hispanic populations[8], although we did not explore potential mechanisms for racial disparities in this study. Of note, we do not endorse race-based medicine and believe that differences seen between races are attributable to factors outside of biology and genetics.

Similarly, our study showed patients with a body mass index greater than 25 were at statistically significant increased risk of COVID-19, regardless of hospitalization status (not shown, $P < 0.001$ for +COVID-19 regardless of hospitalization for both BMI 25–20 and BMI >30). This is also consistent with previous studies showing increased severity of COVID-19 among patients in larger bodies[9]. Again, we note that the mechanism for this risk is not fully understood and may be related to factors outside of biology.

Table 1. Patient Demographics

Characteristic	COVID-19 positive (n = 4528)	COVID-19 negative (n = 162,955)	Total sample (n = 167,483)	P^a
Any of these events occur: pulmonary embolism, cerebral infarction, thromboembolic event (%)	1.4%	1.5%	1.5%	0.517
Age (mean, SD)	48.2 (15.2)	50.5 (15.5)	50.5 (15.5)	<0.001
Female (%)	63.4%	62.2%	62.2%	0.107
Race (%)				
White	85.3%	87.3%	87.2%	<0.001
Black	9.2%	6.9%	7.0%	
Asian	4.0%	4.4%	4.4%	
Other/missing	1.5%	1.5%	1.5%	
Hispanic (%)	1.2%	1.1%	1.1%	0.474
English preferred (%)	95.8%	96.4%	96.4%	0.029
Foreign born (%)	9.8%	8.9%	9.0%	0.037
Partnered (%)	58.2%	58.5%	58.5%	0.707
Neighborhood descriptors (mean, SD)				
Educational distribution				
Less than high school degree	6.7% (6.6%)	6.2% (6.6%)	6.2% (6.6%)	<0.001
High school degree	25.3% (9.9%)	22.9% (10.6%)	23.0% (10.6%)	
Bachelor's degree	22.3% (10.5%)	25.1% (11.4%)	25.1% (11.4%)	
Graduate degree	10.3% (8.0%)	12.9% (9.8%)	12.8% (9.8%)	
Housing				
Crowded	97.6% (3.9%)	97.8% (3.8%)	97.8% (3.8%)	<0.001
No vehicle	6.1% (8.6%)	5.9% (8.5%)	5.9% (8.5%)	0.109
Under FPL	9.4% (7.9%)	8.6% (7.9%)	8.6% (7.9%)	<0.001
Weight status				
Normal (BMI < 25)	19.4%	26.0%	25.8%	<0.001
Overweight (25≤BMI < 30)	30.8%	30.5%	30.5%	
Obese (BMI ≥ 30)	49.8%	43.5%	43.7%	
Chronic condition indicators				
Asthma	12.3%	10.5%	10.6%	<0.001
Cancer	6.8%	9.6%	9.5%	<0.001
COPD	3.1%	3.9%	3.9%	0.005
Diabetes	14.9%	14.6%	14.7%	0.648
Bronchitis	4.4%	3.6%	3.6%	0.006
Chronic respiratory failure	0.4%	0.4%	0.4%	0.837
Emphysema	1.4%	1.6%	1.6%	0.151
Pulmonary disease	0.8%	1.1%	1.1%	0.144
Tobacco use				
Never	56.9%	55.6%	55.6%	<0.001
Current user	12.0%	15.4%	15.3%	
Former user	31.2%	29.0%	29.0%	

Abbreviations: FPL, federal poverty line; SD, standard deviation; BMI, body mass index; COPD, chronic obstructive pulmonary disease.
[a]*P* values document statistical significance of the difference between the COVID-19 positive and control populations. These statistics are computed using Pearson chi-square test for categorical variables, and analyses of variance for continuous variables.

Our data also indicate those with a positive COVID-19 diagnosis not requiring hospitalization were statistically younger, less likely to prefer English and more likely to be foreign born compared with those testing negative for COVID-19. Those with COVID-19 lived in neighborhoods that tended to be less educated and have higher poverty rates. Future research should seek to better

Table 2. Predicting Venous Thromboembolism: The Impact of a Positive COVID-19 Test Without Hospitalization

	Mean	95% CI
Propensity score		
Weighted	0.0010	−0.0210, 0.0231
Unweighted	0.0002	−0.0036, 0.0040

	Weighted		Unweighted	
	Odds ratio	*P*	Odds ratio	*P*
Positive COVID-19 test, not hospitalized	1.0704	0.924	1.0144	0.912
Age	1.0300	<0.001	1.0298	<0.001
Female	0.7674	<0.001	0.7575	<0.001
Race[a]				
Black	1.8613	<0.001	1.8832	<0.001
Asian	1.1307	0.397	1.1058	0.492
Other/missing	1.3870	0.034	1.3760	0.040
Hispanic	1.2032	0.404	1.2216	0.362
English preferred	0.9857	0.922	0.9570	0.766
Foreign born	0.7071	0.002	0.6981	0.002
Partnered	0.8265	<0.001	0.8189	<0.001
Neighborhood descriptors				
Educational distribution[b]				
High school degree	0.9980	0.561	0.9984	0.633
Bachelor's degree	0.9960	0.187	0.9963	0.231
Graduate degree	1.0008	0.800	1.0009	0.779
Housing				
Crowded	0.9997	0.957	0.9997	0.953
No vehicle	1.0031	0.271	1.0032	0.257
Under FPL	0.9989	0.757	0.9989	0.751
Weight status[c]				
Overweight	0.8152	<0.001	0.8163	<0.001
Obese	0.9706	0.565	0.9761	0.643
Chronic condition indicators				
Asthma	1.0675	0.311	1.0689	0.301
Cancer	1.8921	<0.001	1.8847	<0.001
COPD	1.4306	<0.001	1.4142	<0.001
Diabetes	1.5344	<0.001	1.5350	<0.001
Bronchitis	1.1760	0.060	1.2006	0.033
Chronic respiratory disease	1.5830	0.006	1.6088	0.004
Emphysema	1.2804	0.019	1.3050	0.012
Pulmonary disease	2.0220	<0.001	1.9792	<0.001
Smoking status[d]				
Current smoker	1.3651	<0.001	1.3592	<0.001
Former smoker	1.1009	0.043	1.1100	0.028
Constant	0.0035	<0.001	0.0036	<0.001

Abbreviations: FPL, federal poverty line; COPD, chronic obstructive pulmonary disease; CI, confidnce interval.
Notes: The top panel shows the average treatment effect (change in probability of any event due to a positive COVID-19 test). The bottom panel shows the comparison of propensity score weighted and unweighted odds ratios.
[a]White is reference value.
[b]Less than high school was omitted.
[c]Normal is reference value.
[d]Never is reference value.

understand the risks of COVID-19 and the efficacy of public health messaging.

This observational study has some limitations, including the potential for unaccounted factors that may increase the risk for a thromboembolic event such as additional comorbidities not included in the analysis as well as a lack of racial and ethnic diversity in the overall study sample. In addition, we lost about 21% of our observations due to missing data. The vast majority of the lost records (97%) were due to missing body mass indicators and race/ethnicity descriptors. However, if we exclude these variables to retain observations, our results do not change.

Our findings suggest that patients not requiring hospitalization for COVID-19 infection likely would not benefit from prophylactic anticoagulation in the outpatient setting. Additional research should be done to assess the role of COVID-19 vaccination status as well as differences by subvariant in VTE risk. We continue to support published guidelines for starting prophylactic anticoagulation when indicated for patients hospitalized with COVID-19.

To see this article online, please go to: http://jabfm.org/content/35/6/1163.full.

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